REMARKS

The Present Invention

The present invention is directed to a method of reducing the activity of hyperactive T cells. The method comprises contacting hyperactive T cells selected from the group consisting of tumor antigen-specific, transplant-specific, allergen-specific and virus-specific T cells with at least one proteolytic enzyme selected from trypsin and papain and, optionally, rutoside.

The Pending Claims

Claims 9, 11, 13-19, 21 and 23-28 are currently pending. All of the claims are directed to the method.

The Amendments to the Specification and Claims

The specification has been amended to delete the amino acid sequence on page 12, thereby rendering moot the requirement for a Sequence Listing. The deletion of the amino acid sequence does not adversely affect the sufficiency of disclosure inasmuch as the sequence was know in the art prior to the filing of the German application to which this application claims priority and is available to the public in numerous journal articles; etc. as evidenced by the abstracts obtained through PubMed and submitted herewith.

Claim 9 has been amended to recite the limitation of claim 10, which resulted in the cancellation of claims 10, 12, 20 and 22 and the amendment of the dependencies of those claims which originally depended from the cancelled claims. In addition, claim 9 has been amended to recite "reducing the activity" of hyperactive T cells as supported by the data set forth in the specification. Claims 13-18 have been amended to recite "organism" as supported by the specification at, for example, page 1 and the Examples. Further amendments to claims 13-18 serve to address matters of form. Therefore, no new matter has been added by way of the amendments to the claims.

The Office Action

The Office has set forth the following objection and rejections:

(i) the specification has been objected to for recitation of a sequence on page 12 without compliance with one or more of the requirements under 37 C.F.R. § 1.821-1.825,

(ii) claims 13-18 have been rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite,

(iii) claims 9 and 10 have been rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Mynott et al.,

(iv) claims 9 and 10 have been rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Kunze et al.,

(v) claims 9-14, 19 and 20 have been rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Ransberger, and

(vi) claims 9-28 have been rejected under 35 U.S.C. § 103(a) as allegedly obvious in view of and, therefore, unpatentable over Mynott et al., Kunze et al., and Ransberger. Reconsideration of this objection and these rejections is hereby requested.

Discussion of Objection to the Specification

The Office has objected to the specification for recitation of the sequence of amino acids 139-151 of PLP on page 12 of the specification without compliance with one or more of the requirements under 37 C.F.R. § 1.821-1.825. This sequence was known in the art prior to filing of the German application to which this application claims priority, as evidenced by the enclosed PubMed abstracts. Therefore, the amino acid sequence has been deleted from the specification. Accordingly, the objection to the specification is believed to be moot.

Discussion of Rejection under 35 U.S.C. § 112, second paragraph

Claims 13-18 have been rejected under Section 112, second paragraph, as allegedly indefinite. According to the Office, it is unclear how the hyperactive T cells, themselves, are contacted with the specified dose, when the dose is administered to an organism containing the hyperactive T cells. This rejection is believed to be moot in view of the amendments to claims 13-18.

Discussion of Rejections under 35 U.S.C. § 102(b)

Claims 9 and 10 have been rejected under Section 102(b) as allegedly anticipated by Mynott et al. Mynott et al. does not teach, let alone suggest, the use of trypsin or papain as recited in claim 9, and claim 10 has been canceled. Therefore, this rejection should be withdrawn.

Claims 9 and 10 also have been rejected under Section 102(b) as allegedly anticipated by Kunze et al. Kunze et al. does not teach the administration of papain and/or trypsin to reduce the activity of hyperactive T cells. Therefore, Kunze et al. cannot be said to anticipate the rejected claims, and the rejection under Section 102(b) should be withdrawn.

Claims 9-14, 19 and 20 have been rejected under Section 102(b) as allegedly anticipated by Ransberger. Ransberger does not teach the administration of papain and/or trypsin, alone or in further combination with bromelain, rutoside, and/or α_2-macroglobulin, to reduce the activity of hyperactive T cells. Therefore, Ransberger cannot be said to anticipate the rejected claims, and the rejection under Section 102(b) should be withdrawn.

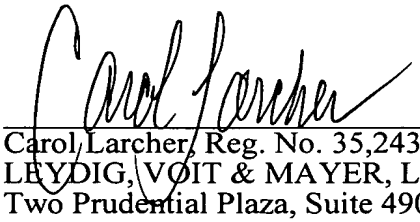
Discussion of Rejection under 35 U.S.C. § 103(a)

Claims 9-28 have been rejected under Section 103(a) as allegedly obvious in view of and, therefore, unpatentable over Mynott et al., Kunze et al. and Ransberger. The cited references, whether taken alone or in various combinations, neither teach, nor reasonably suggest, the administration of papain and/or trypsin, alone or in further combination with bromelain, rutoside, and/or α_2-macroglobulin, to reduce the activity of hyperactive T cells. Therefore, the cited references cannot be said to render obvious the rejected claims, and the rejection under Section 103(a) should be withdrawn.

Conclusion

In view of the above remarks, the application is considered to be in good and proper form for allowance and the Office is respectfully requested to pass this application to issuance. If, in the opinion of the Office, a telephone conference would expedite the prosecution of the instant application, the Office is invited to contact the undersigned attorney.

Respectfully submitted,



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Amendment or ROA - Regular (Revised 7/29/03)

1: J Neuroimmunol. 1992 Jun;38(3):229-40.

Induction of active and adoptive relapsing experimental autoimmune encephalomyelitis (EAE) using an encephalitogenic epitope of proteolipid protein.

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Proteolipid protein (PLP) is a major component of the central nervous system (CNS) myelin membrane and has been shown to induce acute experimental autoimmune encephalomyelitis (EAE) in genetically susceptible animals. Here we describe conditions by which a relapsing-remitting form of EAE can be reliably induced in SJL/J mice either actively immunized with the major encephalitogenic PLP peptide, PLP13-151(S), or following adoptive transfer of PLP139-151(S)-specific T cells. The disease follows a reliable relapsing-remitting course with acute clinical signs first appearing 6-20 days after priming or transfer and relapses first appearing at 30-45 days. The initial onset of disease correlates with delayed-type hypersensitivity (DTH) reactivity specific for PLP139-151(S), in the apparent absence of T cell reactivity to the major myelin basic protein (MBP) peptide. Histologically, both the active and adoptive forms of the disease are characterized by extensive mononuclear cell infiltration and severe demyelination of the CNS. These results suggest that T cell responses specific for PLP139-151(S) are sufficient to induce clinical and histological R-EAE in SJL/J mice. This model should prove useful for examination of the cellular and molecular events involved in clinical relapses and perhaps in determining the role of PLP-specific T cell responses in multiple sclerosis (MS).

PMID: 1376328 [PubMed - indexed for MEDLINE]

1: J Neuroimmunol. 1990 Jan;26(1):9-23.

Class II-restricted T cell responses in Theiler's murine encephalomyelitis virus (TMEV)-induced demyelinating disease. III. Failure of neuroantigen-specific immune tolerance to affect the clinical course of demyelination.

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Intracerebral inoculation of Theiler's murine encephalomyelitis virus (TMEV) into susceptible mouse strains produces a chronic demyelinating disease in which mononuclear cell-rich infiltrates in the central nervous system (CNS) are prominent. Current evidence strongly supports an immune-mediated basis for myelin breakdown, with an effector role proposed for TMEV-specific, major histocompatibility complex (MHC) class II-restricted delayed-type hypersensitivity (DTH) responses in which lymphokine-activated macrophages mediate bystander demyelination. The present study examined the possibility that concomitant or later-appearing neuroantigen-specific autoimmune T cell responses, such as those demonstrated in chronic-relapsing experimental allergic encephalomyelitis (R-EAE), may contribute to the demyelinating process following TMEV infection. T cell responses against intact, purified major myelin proteins (myelin basic protein (MBP) and proteolipid protein (PLP], and against altered myelin constituents were readily demonstrable in SJL/J mice with R-EAE, but were not detectable in SJL/J mice with TMEV-induced demyelinating disease. TMEV-infected mice also did not display T cell responses against the peptide fragments of MBP(91-104) and PLP(139-151) recently shown to be encephalitogenic in SJL/J mice. In addition, induction of neuroantigen-specific tolerance to a heterogeneous mixture of CNS antigens, via the i.v. injection of syngeneic SJL/J splenocytes covalently coupled with mouse spinal cord homogenate, resulted in significant suppression of clinical and histologic signs of R-EAE and the accompanying MBP- and PLP-specific DTH responses. In

contrast, neuroantigen-specific tolerance failed to alter the development of clinical and histologic signs of TMEV-induced demyelinating disease or the accompanying virus-specific DTH and humoral immune responses. These findings demonstrate that TMEV-induced demyelinating disease can occur in the apparent absence of neuroantigen-specific autoimmune responses. The relationship of the present results to the immunopathology of multiple sclerosis is discussed.

PMID: 1688446 [PubMed - indexed for MEDLINE]

1: J Immunol. 1989 Mar 1;142(5):1523-7.

Identification of an encephalitogenic determinant of myelin proteolipid protein for SJL mice.

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PLP is the major protein constituent of central nervous system myelin. We have previously shown that SJL/J (H-2s) mice develop an acute form of EAE after immunization with PLP. The purpose of the present study was to identify an encephalitogenic determinant of PLP for SJL mice. We immunized SJL/J mice with a synthetic peptide identical to residues 130-147 QAHSLERVCHCLGKWLGH of murine PLP, a sequence having an amphipathic alpha-helical conformation. Although it did not induce disease, an overlapping peptide containing residues 139-154 HCLGKWLGHPDKFVGI was encephalitogenic. Immunization with this peptide induced severe clinical and histologic EAE in 3 of 20 mice. T cell enriched ILN cells from these mice responded specifically (3H-thymidine incorporation) to this peptide as well as to shorter analogues of this domain containing serine in place of cysteine at residues 138 and 140. Immunization with the serine-substituted PLP peptides 137-151 VSHSLGKWLGHPDKF and 139-151 HSLGKWLGHPDKF induced severe, acute EAE in 4 of 9 and 15 of 15 SJL mice, respectively, and their T cell enriched ILN cells responded not only to the analogues, but also to the native PLP sequence 139-154. These results indicate that residues 139-151 of murine PLP is an encephalitogenic determinant for SJL mice. Furthermore, like the PLP encephalitogenic domain for SWR (H-2q) mice, this determinant is also a T cell epitope with a coding sequence at the end of an exon.

PMID: 2465343 [PubMed - indexed for MEDLINE]

1: J Neuroimmunol. 1992 Jul;39(1-2):67-74.

Myelin proteolipid protein: minimum sequence requirements for active induction of autoimmune encephalomyelitis in SWR/J and SJL/J mice.

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Proteolipid protein (PLP) is the major protein constituent of mammalian central nervous system myelin. We have previously identified two different PLP encephalitogenic T cell epitopes in two mouse strains. Murine PLP peptides 103-116 YKTTICGKGLSATV and 139-151 HCLGKWLGHPDKF are encephalitogenic determinants in SWR/J (H-2q) and SJL/J (H-2s) mice, respectively. The purpose of the present study was to determine the minimum sequence requirements for each of these PLP encephalitogens. In SWR/J mice, at least two distinct overlapping peptides can induce experimental autoimmune encephalomyelitis (EAE). The eleven residue sequences PLP 105-115 TTICGKGLSAT and PLP 106-116 TICGKGLSATV are encephalitogenic in SWR/J mice, but PLP 106-115 TICGKGLSAT, the decapeptide indigenous to both sequences, is non-encephalitogenic. In contrast, the shortest PLP sequence capable of inducing EAE in SJL/J mice is the nonapeptide 141-149 LGKWLGHPD. These data indicate that encephalitogenic determinants of PLP are short contiguous peptide sequences similar in length and diversity to those of MBP.

PMID: 1377711 [PubMed - indexed for MEDLINE]